UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/759,622	01/12/2001	Karl Tryggvason	TRV 20011-2	3161

7590 11/04/2005

Richard J. Minnich
Fay, Sharpe, Fagan, Minnich & McKee
Suite 700
1100 Superior Avenue
Cleveland, OH 44114-2518

EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 11/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/759,622	TRYGGVASON ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 September 2005* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4,5,11-19,21-32,34-45,47-49 and 51-54* is/are pending in the application.

4a) Of the above claim(s) *4,5,11-18 and 54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19,21-32,34-45,47-49 and 51-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 January 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 21, 2005 has been entered.

Claim Rejections - 35 USC § 112 – Written Description

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 19, 21-25, 27-32, 34-38, 40-45, 47-48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a ``representative number'' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed

by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.)

Claims 19, 21-32, 34-45, 47-48 encompass a genus of NPHS1 proteins or nucleic acids which are different from those disclosed in the specification. In particular, the specification teaches a single NPHS1 sequence, SEQ ID NO: 1 as well as a two examples of mutations of the Nephrin sequence, a deletion of 2 base pairs and a nonsense mutation. However, the claimed genus includes variants for which no written description is provided in the specification. No common element or attributes of the sequences are required by the claims, not even the presence of certain domains. No structural limitations or requirements which provide guidance on the identification of sequences which meet the functional limitation of comprising a "NPHS1" gene is provided. Further, these claims encompass alternately spliced versions of the Nphs1 proteins, as well as allelic variants of Nphs1 including insertions and mutations. The claims also encompass inactive Nphs1 precursor proteins which have a removable amino terminal end, and only the specific amino acid sequence of SEQ ID NO: 2 has been provided by the specification. No written description of alleles, of upstream or downstream regions containing additional sequence, or of alternative splice variants has been provided in the specification. In a gene that is over 4000 nucleotides in length, there are 3^{4000} (or about 3×10^{1908}) possible single point mutations alone, not including the other types of mutations. Thus, applicant has express possession of only two

particular mutations of Nphs1 in a genus which comprises hundreds of millions of different possibilities.

In fact, the claim clearly intends to capture mutations for which no description is provided. The only definition of the mutations is functional, in that the mutations must be in a certain exon or associated with a certain disease. However, aside from the specific mutations taught in the specification, no other mutations are described, in a genus that as noted above is immense.

It is noted in the recently decided case The Regents of the University of California v. Eli Lilly and Co. 43 USPQ2d 1398 (Fed. Cir. 1997) decision by the CAFC that

> "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169- 71, 25 USPQ2d at 1605- 06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372- 73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. "

In the current situation, the definition of Nphs1 in the claims completely lacks any specific structure, and represents precisely the situation of naming a type of material which is generally known to likely exist, but, except for the two specific variants, is in the

absence of knowledge of the material composition and fails to provide descriptive support for the generic claim to "a Nphs1 gene", for example.

It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that

> "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

The current situation is a definition of the compound solely but its functional utility, as a Nphs1 gene or gene deletion, without any definition of the particular variants claimed.

In the instant application, certain specific SEQ ID NOs are described. Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception of any nucleic acids other than those expressly disclosed which comprise Nphs1 or deletions of the Nphs1 gene. Therefore, the claims fail to meet the written description requirement by encompassing sequences which are not described in the specification and which were not in possession of the Applicant.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

5. Claims 19, 21-32, 34-45, 47-49 and 51-53 are rejected under 35 U.S.C. 102(a) as being anticipated by Kestila et al (Mol. Cell (March 1998) 1:575-582)).

Kestila teaches a method of claims 19, 32, 45 for diagnosing congenital nephrotic syndrome comprising detecting a mutation in exons 2 and 26 for a premature stop codon (see page 581, subheading "mutation analysis").

With regard to claim 21, 34, 51, Kestila a 2 basepair deletion (see page 577, column 1).

With regard to claims 22-24, 27-29, 35-37, 40-42, 47-48, 52-53, Kestila teaches PCR amplification with SEQ ID Nos: 3-6(see page 581, subheading "mutation analysis").

With regard to claims 25-26, 38-39, Kestila teaches a single base pair change of CGA-TGA in exon 26 (see page 577, column 2).

With regard to claims 30-31, 43-44, Kestila teaches screening for a novel Dde1 site (see page 581, subheading "mutation analysis").

With regard to claim 49, Kestila teaches comparison of the mutated gene to the control in normal patients in order to determine the presence or absence of a mutation (see page 581, subheading "mutation analysis").

Response to Arguments

6. Applicant's arguments filed September 21, 2005 have been fully considered but they are not fully persuasive.

First, this action is non final since the Kestila reference was newly applied.

Applicant argues that there is a structure function relationship which complies with written description for claims 19, 21-32, 34-45, 47-48 because the claims are limited to particular exons and there are a sufficient number of representative species shown. For claims 26 and 39, limited to specific mutation of CGA-TGA, this argument is persuasive. However, for the generic claims, this argument is not persuasive because one polymorphism is not representative of another polymorphism. Each represents a different change in the nucleic acid. The issue is whether there is any structure function relationship which correlates the function, basement membrane disease, with a particular structure. This question fundamentally addresses the issue of whether there is any structure which the specification demonstrates is necessarily correlated with the function of basement membrane disease. In this case, the answer is no, there is no structure given, other than the two specific polymorphisms, which are associated with congentical Nephrotic Syndrome.

Conceptually, at minimum a polymorphism is a single nucleotide change in a DNA sequence. It may represent a larger change, including a deletion, an insertion or multiple changes, but minimally consists of a single nucleotide change. To describe such a change, both possible nucleotides at the position of interest must be disclosed. It is insufficient to describe a polymorphism as, hypothetically, an Adenine at position

57, because this is not a polymorphism, just a sequence. In order to be a polymorphism, the description must state, for example, a Guanosine for Adenine change at position 57. So the description of a sequence is not a description of a polymorphism, since the sequence alone does not provide the structure of the change that IS the polymorphism.

So instant claim 19, for example, provides no description of any polymorphism whatsoever. Further, the specification provides a description of only two polymorphisms that are associated with basement membrane disease. There is no structure in commone between the specific nucleotide change of a deletion at nucleotide 121 in exon 2 and the CGA-TGA polymorphism in exon 26. More importantly, there is no structure in common between the specific change at either of the disclosed polymorphisms and any other polymorphism which may exist. This is because there is nothing in common between having a G to A change at position 57 and having a C to A change at position 93 or a G to T change at position 105 or even having a G to A change at position 33 (all of which are hypothetical changes). Even the G to A change at position 33 shares no structural relationship with the G to A change at position 57 because each of these changes occurs in distinct sequence regions, with distinct effects and with no necessary relationship. So there is no common structure between polymorphisms.

The presence and existence of the two polymorphisms in the Nephrin sequence shown by Appellant does not even necessarily demonstrate that the Nephrin gene itself is necessarily involved in basement membrane disease and consequently, the structure

of SEQ ID NO: 1 is not necessarily even relevant. These polymorphisms may simply represent markers for another gene that is in linkage disequilibrium with the specific alleles at issue, and the actual gene which is involved in basement membrane disease may be tens of thousands of nucleotides distant from the polymorphisms in the Nephrin gene.

However, Applicant's next argument, regarding claims 49 and 51-53, is found persuasive. Upon reconsideration, claim 49 is simply drawn to screening for mutations, whether any mutations are present or not. The screening assay is fully described. Applicant correctly notes that this claim, unlike the earlier diagnostic claims, does not require identification of mutations to be successful, simply attempted. Therefore, claims 49 and 51-53, along with claims 26 and 39, are no longer subject to the written description rejection.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jeffrey Fredman
Primary Examiner
Art Unit 1637
11/2/05